[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

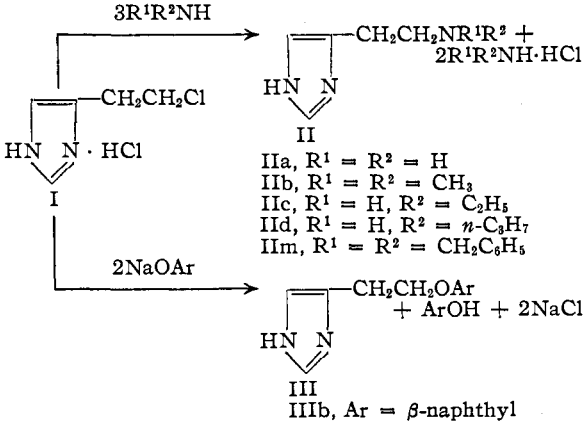
Studies of Imidazole Compounds. IV. Derivatives of 4-Ethylimidazole

BY CHARLES F. HUEBNER, ROBERT A. TURNER AND CAESAR R. SCHOLZ

In the first paper of this series certain derivatives of 4-methylimidazole[1] were discussed; a practicable synthesis of 4-(2-chloroethyl)-imidazole hydrochloride (I)[2] was reported in a later paper. In the present paper derivatives of 4-ethylimidazole related to histamine and prepared from I are described.

Several histamine derivatives bearing alkyl substituents on the side chain nitrogen-atom have been prepared, thus extending the work of Garforth and Pyman[3] who described three lower members of the series. The 4-(2-alkylaminoethyl)-imidazoles (II) were prepared by the addition of I to an excess of an amine in boiling anhydrous *n*-propanol. Some of the condensation products could then be isolated as the dihydrochloride or dihydrobromide. Usually, however, this procedure was not possible; instead, the sirupy dihydrochloride was converted into the crystalline dipicrate, which after suitable purification was reconverted into the crystalline dihydrochloride.

Two substituted 4-ethyl-imidazoles containing oxygen in the side chain (III) were synthesized by reaction of I with a sodium phenolate.



A detailed report on the pharmacology of these imidazoles will be published elsewhere. However, a few remarks in regard to their activity may be in order. In group II, the larger the N-alkyl substituent, the smaller is the histamine activity as measured by the spasm produced on the isolated guinea-pig ileum strip. Following this generalization, the most potent derivatives are 4-(2-dimethylaminoethyl)-imidazole (IIb) and 4-(2-ethylaminoethyl)-imidazole (IIc), each being 75% as active as histamine (IIa).[4] A compound of intermediate activity is IId with 5% of the activity of histamine, whereas IIm, containing the N-benzyl substituent, the largest in the series, is totally inactive at the levels tested (200 times the level at which histamine gave a standard response). Moreover, an interesting example of competitive inhibition is presented by IIm, since it possesses weak but definite antihistaminic activity [0.5% of the activity of N,N-dimethyl-N'-benzyl-N'-(2-pyridyl)-ethylenediamine hydrochloride].

In the series containing an oxygen substituent in the side chain, the pharmacological properties of 4-[2-(2-naphthoxy)-ethyl]-imidazole (IIIb) are worthy of note. It displays a high histamine-like activity, 50% that of histamine, but unlike the latter's action the spasm produced on the ileum strip is only momentary.

Acknowledgment.—The authors take pleasure in expressing appreciation to Dr. B. N. Craver for the pharmacological data and to Mrs. Katheryn Oney for assistance in the laboratory.

Experimental[5]

Physical and analytical data and the methods of preparation are summarized in Table I.

4-(2-Ethylaminoethyl)-imidazole Dihydrochloride (IIc). Procedure A.—A solution of 3.5 g. of I[2] in 30 ml. of a 30% ethanolic ethylamine solution was heated in a sealed tube at 100° for fourteen hours. The product was treated with a solution of 5 g. of sodium carbonate in 25 ml. of water and concentrated *in vacuo*. The residue was heated at 90° *in vacuo* for one hour and then digested with 50 ml. of absolute ethanol and filtered. After several more digestions the combined alcohol solutions were concentrated *in vacuo*. The resulting brown sirup was acidified (congo paper) with 1 *N* hydrochloric acid and added with stirring to a solution of 11.5 g. of picric acid in 150 ml. of water. The crystalline picrate which formed on cooling was recrystallized from water after a treatment with charcoal (Nuchar); yield 8.0 g.; m. p. 185°, with loss of water of crystallization at 104°.

The picrate was converted into the hydrochloride by treating it with 20 ml. of 5 *N* hydrochloric acid and removing the picric acid by repeated extractions with ether. The aqueous layer was concentrated *in vacuo* to a sirup, which after solution in hot methanol crystallized as platelets on careful addition of methyl ethyl ketone; after another crystallization the dihydrochloride weighed 1.5 g., m. p. 162–163°.

4-(2-Diethylaminoethyl)-imidazole Dihydrochloride. Procedure B.—To a stirred solution of 13.4 g. of anhydrous diethylamine in 25 ml. of anhydrous *n*-propanol, boiling under reflux, was added a solution of 3.4 g. of I in 25 ml. of *n*-propanol during one-half hour with exclusion of moisture. After further boiling under reflux for six hours, a solution of 5 g. of sodium carbonate in 25 ml. of water was added and the crude, brown sirupy base isolated as described above. It was treated with a 3 *N* solution of hydrogen chloride in absolute ethanol until strongly acid and crystallization induced by the slow addition of dry ethyl acetate. Recrystallization from dry ethanol–ethyl acetate yielded 0.60 g. of the dihydrochloride, m. p. 219–220°.

(1) Turner, Huebner and Scholz, THIS JOURNAL, 71, 2801 (1949).

(2) Turner, *ibid.*, 71, 3476 (1949).

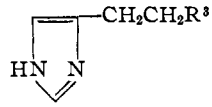
(3) Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

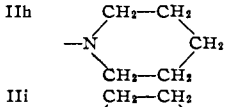
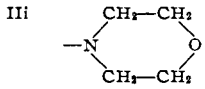
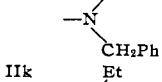
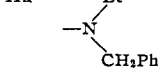
(4) Vartiainen, *J. Pharm. and Exp. Thera.*, 54, 265 (1935), reported the former to be 20% and the latter 5 % as potent as histamine.

(5) The microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J.

TABLE I

DERIVATIVES OF 4-ETHYL-IMIDAZOLE



No.	R^3	Salts	M. p.,[a] °C.	Yield, %	Recrystn. solvent	Procedure	Empirical formula	Analyses, % Calculated C	Calculated H	Found C	Found H
IIb	$-NMe_2$	Dihydrochloride	183–184[b]	25	Ethanol		$C_7H_{13}N_3 \cdot 2HCl$	39.63	7.12	39.95	7.18
		Dipicrate	215[c]	40	Water	A	$C_7H_{13}N_3 \cdot 2C_6H_3O_7N_3$	38.19	3.22	38.01	3.25
IIc	$-NHEt$	Dihydrochloride	162–163[d]	35	Ethanol–acetone	A	$C_7H_{13}N_3 \cdot 2HCl$	39.63	7.12	39.55	7.20
		Dipicrate	(104) 185[e]	60	Water		$C_7H_{13}N_3 \cdot 2C_6H_3O_7N_3$	38.19	3.22	37.93	3.00
IId	$-NHPr$	Dihydrochloride	96–100	50	Ethanol–butanone	A	$C_8H_{15}N_3 \cdot 2HCl$	42.56	7.61[f]	42.68	7.72
		Dipicrate	165		Water		$C_8H_{15}N_3 \cdot 2C_6H_3O_7N_3$	39.27	3.47	39.16	3.50
IIe	$-NHCH(CH_3)_2$	Dihydrochloride	195–196[g]	35	Ethanol–butanone	A	$C_8H_{15}N_3 \cdot 2HCl$	42.56	7.61[h]	42.84	7.69
		Dipicrate	175		Water						
IIf	$-NEt_2$	Dihydrochloride	219–220	15	Ethanol–ethyl acetate	B	$C_9H_{17}N_3 \cdot 2HCl$	45.00	7.97[i]	44.75	7.71
IIg	$-NPr_2$	Dihydrochloride	(Sirup)								
		Dipicrate	190	45	Water	B	$C_{11}H_{21}N_3 \cdot 2C_6H_3O_7N_3$	42.25	4.18	42.16	3.92
IIh		Dihydrochloride	276–278	55	Ethanol–butanone		$C_{10}H_{17}N_3 \cdot 2HCl$	47.60	7.63	47.46	7.24
		Dipicrate	188–191		Water	B	$C_{10}H_{17}N_3 \cdot 2C_6H_3O_7N_3$	41.44	3.64	41.72	3.91
IIi		Dihydrochloride	238–243	55	Ethanol–ether	B	$C_9H_{15}N_3O \cdot 2HCl \cdot {}^1/_2 H_2O$	41.04	6.92	41.26	6.41
IIj		Dihydrobromide	178–179	20	Propanol	C	$C_{12}H_{17}N_3 \cdot 2HBr$	41.40	5.08[j]	41.26	4.83
IIk		Dihydrobromide	82–83	5	Ethanol–butanone	C	$C_{14}H_{19}N_3 \cdot 2HBr$	42.86	5.42	42.70	5.41
IIm	$-N(CH_2Ph)_2$	Dihydrochloride	155–156	15	Propanol	D	$C_{19}H_{21}N_3 \cdot 2HCl \cdot {}^3/_4H_2O$	60.40	6.54	60.44	6.64
IIIa	$-OPh$	Hydrochloride	136–137[k]	40	Ethanol–ether						
		Picrate	118–120[l]	60	Water	E	$C_{11}H_{12}N_2O \cdot C_6H_3O_7N_3$	48.91	3.63	49.05	3.67
IIIb	$-O(2)C_{10}H_7$	.....	151–152								
			(free base)	25	Ethanol	E	$C_{15}H_{14}ON_2$	75.60	5.89	75.61	6.07

[a] Melting points are uncorrected and were taken in a capillary. [b] Reported[3] m. p. 188° cor. [c] Reported[3] m. p. 233° cor. [d] Reported by Garforth and Pyman[3] as m. p. 169° cor. [e] Change in crystalline form at 104° with loss of water of crystallization. Reported m. p. 186° changing at 100° cor. [f] *Anal.* Calcd.: Cl, 31.37. Found: Cl, 31.63. [g] Since the completion of this work, this compound has been synthesized by another method by Sheehan and Robinson, THIS JOURNAL, **71**, 1436 (1949), who report a melting point of 197.5–199° cor. [h] *Anal.* Calcd.: Cl, 31.37. Found: Cl, 31.63. [i] *Anal.* Calcd.: N, 17.50; Cl, 29.52. Found: N, 17.24; Cl, 29.89. [j] *Anal.* Calcd.: N, 11.14; Br, 42.38. Found: N, 11.03; Br, 42.17. [k] Reported m. p. 136–137° cor. [l] Reported m. p. 122° cor.

4-(2-Benzylmethylaminoethyl)-imidazole Dihydrobromide. Procedure C.—The mixture resulting from the reaction of 3.4 g. of I with 10.0 g. of benzylmethylamine, carried out as described under procedure B, was concentrated *in vacuo*. The residue was treated with 50 ml. of 10% aqueous sodium carbonate and extracted with 100 ml. of ether. The ether was removed and the resulting oil distilled at 15 mm. in a bath held at 140–150°. This served to remove most of the benzylmethylamine. A solution of the residue in 10 ml. of 48% hydrobromic acid was taken to dryness *in vacuo*, then dissolved in a few ml. of hot absolute ethanol. The crystalline dihydrobromide obtained after several days in the cold was recrystallized from anhydrous *n*-propanol to yield 1.5 g., m. p. 178–179°.

4-(2-Dibenzylaminoethyl)-imidazole Dihydrochloride Procedure D.—The reaction mixture obtained from 3.4 g. of I and 12.0 g. of dibenzylamine according to procedure B was boiled under reflux for twenty-four hours. The cooled solution ultimately deposited 6.2 g. of dibenzylamine hydrochloride (m. p. 257–258°), which was filtered. After evaporation of the filtrate to dryness, the residue was digested briefly with 1.86 g. of sodium carbonate in 30 ml. of water. Repeated extraction of the aqueous suspension with petroleum ether removed dibenzylamine, and the crude imidazole was extracted with diethyl ether. Following distillation of the ether, the residue was dissolved in 10 ml. of concentrated hydrochloric acid, evaporated to dryness, and dissolved in 10 ml. of ethanol. When this solution was left in the cold for several hours, it deposited 1.4 g. of dibenzylamine hydrochloride, which was filtered. The evaporated filtrate was taken up in 5 ml. of hot anhydrous *n*-propanol. The solution yielded 1.5 g. of crude 4-(2-dibenzylaminoethyl)-imidazole dihydrochloride; after two more recrystallizations 0.36 g. of the pure hydrochloride remained, m. p. 155–156°.

4-(2-Phenoxyethyl)-imidazole Dihydrochloride. Procedure E.—To a solution of 2.8 g. of phenol in 23.0 ml. of 1.30 *N* methanolic sodium methoxide, boiling under reflux, was slowly added a solution of 2.5 g. of I in 25 ml. of *n*-propanol. After six hours the cooled reaction mixture was treated with an excess of 3 *N* hydrogen chloride in ethanol, the precipitated sodium chloride was collected, and the filtrate was taken to dryness *in vacuo*. The residue was suspended in water and extracted several times with ether to remove excess phenol. The aqueous phase was added to a boiling solution of 8.5 g. of picric acid in 130 ml. of water. The picrate was filtered and recrystallized from water; yield 4.2 g., m. p. 118–120°. The picrate was converted into the hydrochloride by treating it with 12 *N* hydrochloric acid and extracting with ether in the usual manner. The sirupy hydrochloride was recrystallized from absolute ethanol–ether; m. p. 129–131°; yield 1.3 g.

Summary

A series of 4-(2-alkylaminoethyl)-imidazoles

related to histamine and two 4-(2-aryloxyethyl)-imidazoles have been prepared from 4-(2-chloroethyl)-imidazole hydrochloride. A few of these substances resembled histamine in their pharmacodynamic actions but all were less active. Weak antihistaminic activity was shown by 4-(2-dibenzylaminoethyl)-imidazole.

SUMMIT, N. J. RECEIVED JUNE 18, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, GENERAL MILLS, INC.]

Polyglycerols. III.[1] Synthesis of Triglycerol[2]

BY J. ROBERT ROACH AND HAROLD WITTCOFF

The synthesis of a crystalline isomer of linear triglycerol[3] is described in this paper.

Probably the first reference to triglycerol was made by Lourenco[4] who reported it as a distillable reaction product from the interaction of glycerol and gaseous hydrogen chloride. Levene and Walti[5] hydrolyzed the reaction products resulting from the action of potassium acetate on epichlorohydrin to obtain several distillable products including a small quantity of triglycerol (b. p. 200–205° (0.1 mm.)). The same boiling range was reported by Istin[6] who distilled triglycerol directly from a polyglycerol mixture. Isolation of crude triglycerol from a polyglycerol mixture by distillation of the acetates[7,8] and the allyl ethers[9] has also been reported. In none of this work has the crystalline pentahydric triglycerol been isolated.

The present synthesis involves the hydroxylation of O-α,α'-diallylglycerol[9] by action of either performic acid or potassium permanganate. The requisite diallylglycerol was prepared by the interaction of allyl alcohol and glycerol-α,α'-dichlorohydrin in the presence of sodium hydroxide. The homogeneity of this product, on which depends the linear structure of the triglycerol, follows from the oft-recorded observation that chlorohydrins such as glycerol dichlorohydrin are dehydrohalogenated in strong basic medium to epoxides. These, in turn, react with alcohols to yield ethers in which the ether linkage is primary.[10] Furthermore, it was not possible by careful fractional distillation to detect the presence of any isomeric substance.

Since the triglycerol could not be readily distilled from the reaction mixtures in which it was formed, acetonation was employed. On treatment of the crude mixtures with acidic acetone, there resulted a mixture of isopropylidenetriglycerol and diisopropylidenetriglycerol which on hydrolysis yielded the pure triglycerol.

Separation of isopropylidenetriglycerol and diisopropylidenetriglycerol was difficult. By careful fractional distillation, however, samples which analyzed properly were obtained.

The triglycerol obtained by hydrolysis of the isopropylidene derivatives was probably a sirupy mixture of stereoisomers. Crystallization from anhydrous *n*-butanol of the product resulting from performic acid hydroxylation yielded 25–33% of a crystalline isomer of melting point 98–99°. The sirup from the mother liquor could not be induced to crystallize. For linear triglycerol there are theoretically possible a *dl*-mixture and two *meso*-forms. The presence of isomers was perhaps indicated by the fact that the sirupy triglycerol from the performic acid hydroxylation demonstrated proper elementary analyses. That permanganate hydroxylation provided a different ratio of isomers was inferred from the observation that the sirupy triglycerol yielded, on crystallization, 50% of crystalline isomer of identical melting point.

The solid triglycerol was converted to the penta-(*p*-nitrobenzoate) derivative. Attempts to prepare similar derivatives of the sirupy isomers from which the crystalline triglycerol had been removed led only to uncrystallizable oils.

Experimental

O-α,α'-Diallylglycerol.—Allyl alcohol (1161 g., 20 moles) was added, with stirring, to 50% aqueous sodium hydroxide (880 g., 11 moles) whereupon the temperature rose spontaneously to 52°. Glycerol dichlorohydrin (644.8 g., 5 moles) was added dropwise over a period of three and one-fourth hours, while the temperature was maintained at 70–80° by the exothermic reaction. After completion of the addition, stirring was continued at 70–80° for one and one-fourth hours, whereupon the excess allyl alcohol was removed by distillation *in vacuo*. The product was washed successively with water, dilute acetic acid, and again with water until the washings were neutral. All of the aqueous solutions were combined and extracted with ether, after which the ether solution was washed with water and was combined with the product. The mixture was dried (sodium sulfate) and after removal of the ether, the product was distilled through a 15-inch Vigreux column. No forerun was obtained. The material of constant refractive index ($n^{25}D$ 1.4520, d^{25}_4 0.9810) distilled at 112–113° (14 mm.) and weighed 524.4 g. (60.8%). Redistillation at high reflux ratio through a 12-inch column packed with stainless steel helices gave a series of

(1) Paper II, THIS JOURNAL, **71**, 2666 (1949).

(2) Paper No. 100, Journal Series, Research Laboratories, General Mills, Inc.

(3) For a discussion of nomenclature *cf.* H. Wittcoff, J. R. Roach and S. E. Miller, THIS JOURNAL, **69**, 2655 (1947), footnote 2.

(4) A. V. Lourenco, *Ann. chim. phys.*, [3] **67**, 257 (1863).

(5) P. A. Levene and A. Walti, *J. Biol. Chem.*, **77**, 685 (1928).

(6) M. Istin, *Ann. faculté sci. Marseille*, **13**, 5 (1940); *C. A.*, **41**, 2392 (1947).

(7) M. Rangier, *Compt. rend.*, **187**, 345 (1928); *C. A.*, **22**, 4468 (1928).

(8) H. J. Wright and R. N. DuPuis, THIS JOURNAL, **68**, 446 (1946).

(9) N. Kishner, *J. Russ. Phys.-Chem. Soc.*, [1] 31 (1892); Beilstein, "Handbuch der organische Chemie," 4th ed., J. Springer, Berlin, 1918, Vol. I, p. 513.

(10) A. Fairbourne, G. P. Gibson and D. W. Stephens, *J. Chem. Soc.*, 1965 (1932).